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01/10 2003 16:08 FAX 858 720 2553 PAUL HASTINGS 001

Paul, Hastings, Janofsky & Walker LLP
3579 Valley Centre Drive, San Diego, CA 92130
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Paul Hastings

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from:	facsimile:	telephone:	initials:
Diana L. Bush, Ph.D., Esq.	(858) 720-2555	(858) 720-2885	DLB4

client name: Metabasis Therapeutics, Inc. client matter number: 45198.00027.CON1

date: October 1, 2003 pages (with cover): 24

to:	company/office:	facsimile:	telephone:
Examiner Dameron Jones Art Unit 1616	USPTO	703 872-9306	703 308-4640

comments:

U. S. Patent Application No. 09/978,454
NOVEL PRODRUGS FOR PHOSPHORUS-CONTAINING COMPOUNDS
Applicant: Erion, et al.
Filing Date: October 15, 2001
Our Ref: 45198.00027.CON1

Attached hereto are the following documents for filing in the above patent application:
1. Fee Transmittal Sheet
2. Petition for Extension of Time & Response to Office Action
3. Terminal Disclaimer under 37 C.F.R. §1.321(B)

CERTIFICATE OF TRANSMISSION
(37 C.F.R. §1.8)

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3579 Valley Centre Drive, San Diego, CA 92130
telephone 858-720-2500 / facsimile 858-720-2555 / www.paulhastings.com

Paul Hastings

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from:	facsimile:	telephone:	initials:
Diana L. Bush, Ph.D., Esq.	(858) 720-2555	(858) 720-2885	DLB4

client name: Metabasis Therapeutics, Inc. client matter number: 45198.00027.CON1

date: October 1, 2003 pages (with cover): 24

to:	company/office:	facsimile:	telephone:
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Applicant: Erion, et al.
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PaulHastings

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from:	facsimile:	telephone:	initials:
Diana L. Bush, Ph.D., Esq.	(858) 720-2555	(858) 720-2885	DLB4

client name: Metabasis Therapeutics, Inc. **client matter number:** 45198.00027.CON1

date: October 1, 2003 **pages (with cover):** 24

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PTO/SB/17 (05-03)
Approved for use through 04/30/2003. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

FEE TRANSMITTAL for FY 2003

Effective 01/01/2003. Patent fees are subject to annual revision.

☐ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT ($) 1,040.00

Complete if Known	
Application Number	09/978,454
Filing Date	October 15, 2001
First Named Inventor	Erion, et al.
Examiner Name	Dameron Jones
Art Unit	1616
Attorney Docket No.	45198.00027.CON1

METHOD OF PAYMENT *(check all that apply)*

☐ Check ☐ Credit card ☐ Money Order ☐ Other ☐ None

☑ Deposit Account:

Deposit Account Number: 50-2613

Deposit Account Name:

The Director is authorized to: *(check all that apply)*

☑ Charge fee(s) indicated below ☑ Credit any overpayments

☑ Charge any additional fee(s) during the pendency of this application

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FEE CALCULATION

1. BASIC FILING FEE

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1001	750	2001	375	Utility filing fee	
1002	330	2002	165	Design filing fee	
1003	520	2003	260	Plant filing fee	
1004	750	2004	375	Reissue filing fee	
1005	160	2005	80	Provisional filing fee	

SUBTOTAL (1) ($) 0

2. EXTRA CLAIM FEES FOR UTILITY AND REISSUE

	Extra Claims		Fee from below	Fee Paid
Total Claims		-20** =	X	= 0
Independent Claims		- 3** =	X	= 0
Multiple Dependent				=

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description
1202	18	2202	9	Claims in excess of 20
1201	84	2201	42	Independent claims in excess of 3
1203	280	2203	140	Multiple dependent claim, if not paid
1204	84	2204	42	** Reissue independent claims over original patent
1205	18	2205	9	** Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) ($) 0

**or number previously paid, if greater; For Reissues, see above

FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1051	130	2051	65	Surcharge - late filing fee or oath	
1052	50	2052	25	Surcharge - late provisional filing fee or cover sheet	
1053	130	1053	130	Non-English specification	
1812	2,520	1812	2,520	For filing a request for *ex parte* reexamination	
1804	920*	1804	920*	Requesting publication of SIR prior to Examiner action	
1805	1,840*	1805	1,840*	Requesting publication of SIR after Examiner action	
1251	110	2251	55	Extension for reply within first month	
1252	410	2252	205	Extension for reply within second month	
1253	930	2253	465	Extension for reply within third month	930.00
1254	1,450	2254	725	Extension for reply within fourth month	
1255	1,970	2255	985	Extension for reply within fifth month	
1401	320	2401	160	Notice of Appeal	
1402	320	2402	160	Filing a brief in support of an appeal	
1403	280	2403	140	Request for oral hearing	
1451	1,510	1451	1,510	Petition to institute a public use proceeding	
1452	110	2452	55	Petition to revive - unavoidable	
1453	1,300	2453	650	Petition to revive - unintentional	
1501	1,300	2501	650	Utility issue fee (or reissue)	
1502	470	2502	235	Design issue fee	
1503	630	2503	315	Plant issue fee	
1460	130	1460	130	Petitions to the Commissioner	
1807	50	1807	50	Processing fee under 37 CFR 1.17(q)	
1806	180	1806	180	Submission of Information Disclosure Stmt	
8021	40	8021	40	Recording each patent assignment per property (times number of properties)	
1809	750	2809	375	Filing a submission after final rejection (37 CFR 1.129(a))	
1810	750	2810	375	For each additional invention to be examined (37 CFR 1.129(b))	
1801	750	2801	375	Request for Continued Examination (RCE)	
1802	900	1802	900	Request for expedited examination of a design application	

Other fee (s) _ Terminal Disclaimer 110.00

*Reduced by Basic Filing Fee Paid

SUBTOTAL (3) ($) 1,040.00

SUBMITTED BY				(Complete *(if applicable)*	
Name (Print/Type)	Diana L. Bush, Ph.D., Esq.	*Registration No. (Attorney/Agent)*	51,109	*Telephone*	858 720-2500
Signature	Diana L Bush			*Date*	October 1, 2003

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Erion *et al.*	
Serial No.: 09/978,454	Group Art Unit: 1616
Filed: October 15, 2001	Examiner: Dameron Jones
Title: NOVEL PRODRUGS FOR PHOSPHORUS-CONTAINING COMPOUNDS	

AMENDMENT AND REMARKS
&
PETITION FOR EXTENSION OF TIME

Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Applicants hereby petition for a 3-month extension of time under 37 CFR § 1.136(a). With the granting of said extension, it is believed that this response is timely filed. The Commissioner is hereby authorized to charge Deposit Account No. 50-2613 for the 3–month extension fee due herein and any other fees that may become due or credit become payable during the pendency of this application. The amendment and response address the issues raised by the Examiner in an Office Action, dated April 1, 2003.

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October 1, 2003
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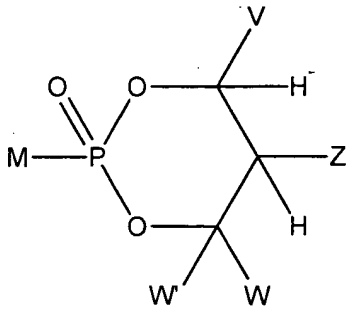
AMENDMENT

In the claims:

Please amend the claims as indicated below. A complete set of all claims previously submitted, including the status for each claim, immediately follows below.

1.-167. (Cancelled)

168. (Previously added) A pharmaceutical composition comprising a compound of Formula I:



Formula I

wherein:

V, W and W' are independently selected from the group consisting of hydrogen, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 atoms, wherein the cyclic group optionally contains one heteroatom and is substituted with a hydroxy, acyloxy, alkoxycarbonyloxy, or aryloxycarbonyloxy group attached to a carbon atom that is three atoms away from both oxygen atoms that are attached to the phosphorus atom; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group wherein the cyclic group optionally contains one heteroatom, and is fused to an aryl group, at the beta and gamma position to the oxygen attached to the phosphorus; or

together V and W are connected via an additional three carbon atoms to form an optionally substituted cyclic group containing six carbon atoms and is optionally substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxycarbonyloxy, alkylthiocarbonyloxy, and aryloxycarbonyloxy groups, wherein such substituent is attached to one of said carbon atoms that is three atoms away from an oxygen attached to the phosphorus atom; or

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

together W and W' are connected via an additional 2-5 atoms to form a cyclic group, optionally containing 0-2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl; or

Z is selected from $-CHR^2OH$, $-CHR^2OC(O)R^3$, $-CHR^2OC(S)R^3$, $-CHR^2OC(S)OR^3$, $-CHR^2OC(O)SR^3$, $-CHR^2OCO_2R^3$, $-OR^2$, $-SR^2$, $-CHR^2N_3$, $-CH_2$(aryl), $-CH$(aryl)OH, $-CH(CH=CR^2_2)OH$, $-CH(C\equiv CR^2)OH$, $-R^2$, $-NR^2_2$, $-OC(O)R^3$, $-OCO_2R^3$, $-SC(O)R^3$, $-SCO_2R^3$, $-NHC(O)R^2$, $-NHCO_2R^3$, $-CH_2NH$(aryl), $-(CH_2)_pOR^{12}$, and $-(CH_2)_pSR^{12}$;

R^2 is selected from the group consisting of R^3 and hydrogen;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

R^{12} is selected from the group consisting of hydrogen, and lower acyl; and

p is an interger 2 or 3;

with the provisos that:

a) V, Z, W, and W' are not all hydrogen; and

b) when Z is $-R^2$, then at least one of V, W, and W' is not hydrogen, alkyl, aralkyl, or alicyclic; and

M is selected from the group that, attached to PO_3^{2-}, $P_2O_6^{3-}$, or $P_3O_9^{4-}$, is biologically active *in vivo* and that is attached to the phosphorus atom in Formula I via a carbon, oxygen, or nitrogen atom, with the proviso that $M\text{-}PO_3^{2-}$ is not an FBPase inhibitor;

wherein said compound of Formula I is converted to MPO_3H_2 by human liver microsomes;

pharmaceutically acceptable salts of Formula I;

and a pharmaceutically acceptable excipient.

169. (Previously Amended) The pharmaceutical composition of claim 168, wherein MH is 9-(2-phosphonylmethoxyethyl)adenine (PMEA) or analogues thereof.

170. (Previously Amended) The pharmaceutical composition of claim 168, wherein MH is 9-(2-phosphonylmethoxyethyl)adenine (PMEA).

171. (Previously Amended) The pharmaceutical composition of claim 168, wherein MH is selected from penciclovir, 3TC, ACV, PMPA, araC, ribavirin, fludarabine, and 5-fluoro-2'-deoxyuridine.

172. (Previously Amended) The pharmaceutical composition of claim 168, wherein MH is radiolabelled 2'-deoxy-5-Iodouridine.

173. (Previously Amended) The pharmaceutical composition of claim 172 wherein MH is 2'-deoxy-5-^{131}I-iodouridine.

174. (Previously Amended) The pharmaceutical composition of claim 168, wherein V is selected from the group consisting of aryl, substituted aryl, heteroaryl, and substituted heteroaryl.

175. (Previously Amended) The pharmaceutical composition of claim 168, wherein the prodrug is in the *cis* configuration.

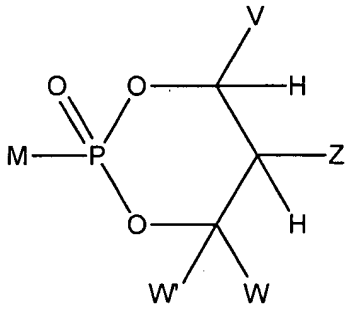
176. (Previously Amended) The pharmaceutical composition of claim 174, wherein the prodrug is in the *cis* configuration.

177. (Previously Amended) The pharmaceutical composition of Claim 171, wherein MH is araC and V is a heteroaryl group.

178. (Previously Amended) The pharmaceutical composition of claim 177, wherein V is 4-pyridyl.

179. (Previously Amended) The pharmaceutical composition of claim 172 wherein MH is 2'-deoxy-5-^{125}I-iodouridine.

180. (Previously added) A pharmaceutical composition comprising a compound of Formula I:



Formula I

wherein:

V, W and W' are independently selected from the group consisting of hydrogen, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and

1-alkynyl; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 atoms, wherein the cyclic group optionally contains one heteroatom and is substituted with a hydroxy, acyloxy, alkoxycarbonyloxy, or aryloxycarbonyloxy group attached to a carbon atom that is three atoms away from both oxygen atoms that are attached to the phosphorus atom; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group wherein the cyclic group optionally contains one heteroatom, and is fused to an aryl group, at the beta and gamma position to the oxygen attached to the phosphorus; or

together V and W are connected via an additional three carbon atoms to form an optionally substituted cyclic group containing six carbon atoms and is optionally substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxycarbonyloxy, alkylthiocarbonyloxy, and aryloxycarbonyloxy groups, wherein such substituent is attached to one of said carbon atoms that is three atoms away from an oxygen attached to the phosphorus atom; or

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

together W and W' are connected via an additional 2-5 atoms to form a cyclic group, optionally containing 0-2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl; or

Z is selected from $-CHR^2OH$, $-CHR^2OC(O)R^3$, $-CHR^2OC(S)R^3$, $-CHR^2OC(S)OR^3$, $-CHR^2OC(O)SR^3$, $-CHR^2OCO_2R^3$, $-OR^2$, $-SR^2$, $-CHR^2N_3$, $-CH_2$(aryl), $-CH$(aryl)OH, $-CH(CH{=}CR^2{}_2)OH$, $-CH(C{\equiv}CR^2)OH$, $-R^2$, $-NR^2{}_2$, $-OC(O)R^3$, $-OCO_2R^3$, $-SC(O)R^3$, $-SCO_2R^3$, $-NHC(O)R^2$, $-NHCO_2R^3$, $-CH_2NH$(aryl), $-(CH_2)_pOR^{12}$, and $-(CH_2)_pSR^{12}$;

R^2 is selected from the group consisting of R^3 and hydrogen;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

R^{12} is selected from the group consisting of hydrogen, and lower acyl; and

p is an interger 2 or 3;

with the provisos that:

a) V, Z, W, and W' are not all hydrogen; and

b) when Z is $-R^2$, then at least one of V, W, and W' is not hydrogen, alkyl, aralkyl, or alicyclic; and

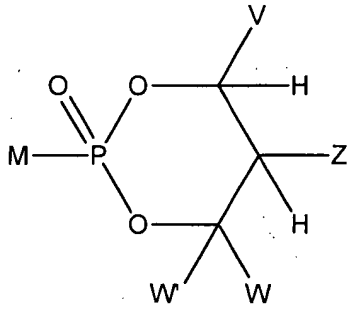
M is selected from the group that, attached to PO_3^{2-}, $P_2O_6^{3-}$, or $P_3O_9^{4-}$, is biologically active *in vivo* and that is attached to the phosphorus atom in Formula I via a carbon atom, with the proviso that MPO_3^{2-} is not an FBPase inhibitor;

wherein said compound of Formula I is converted to MPO_3H_2 by human liver microsomes;

pharmaceutically acceptable prodrugs and salts of Formula I;

and a pharmaceutically acceptable excipient.

181. (Previously added) A pharmaceutical composition comprising a compound of Formula I:



Formula I

wherein:

V, W and W' are independently selected from the group consisting of hydrogen, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 atoms, wherein the cyclic group optionally contains one heteroatom and is substituted with a hydroxy, acyloxy, alkoxycarbonyloxy, or aryloxycarbonyloxy group attached

to a carbon atom that is three atoms away from both oxygen atoms that are attached to the phosphorus atom; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group wherein the cyclic group optionally contains one heteroatom, and is fused to an aryl group, at the beta and gamma position to the oxygen attached to the phosphorus; or

together V and W are connected via an additional three carbon atoms to form an optionally substituted cyclic group containing six carbon atoms and is optionally substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxycarbonyloxy, alkylthiocarbonyloxy, and aryloxycarbonyloxy groups, wherein such substituent is attached to one of said carbon atoms that is three atoms away from an oxygen attached to the phosphorus atom; or

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

together W and W' are connected via an additional 2-5 atoms to form a cyclic group, optionally containing 0-2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl; or

Z is selected from $-CHR^2OH$, $-CHR^2OC(O)R^3$, $-CHR^2OC(S)R^3$, $-CHR^2OC(S)OR^3$, $-CHR^2OC(O)SR^3$, $-CHR^2OCO_2R^3$, $-OR^2$, $-SR^2$, $-CHR^2N_3$, $-CH_2$(aryl), $-CH$(aryl)OH, $-CH(CH{=}CR^2_2)OH$, $-CH(C{\equiv}CR^2)OH$, $-R^2$, $-NR^2_2$, $-OC(O)R^3$, $-OCO_2R^3$, $-SC(O)R^3$, $-SCO_2R^3$, $-NHC(O)R^2$, $-NHCO_2R^3$, $-CH_2NH$(aryl), $-(CH_2)_pOR^{12}$, and $-(CH_2)_pSR^{12}$;

R^2 is selected from the group consisting of R^3 and hydrogen;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

R^{12} is selected from the group consisting of hydrogen, and lower acyl; and

p is an interger 2 or 3;

with the provisos that:

a) V, Z, W, and W' are not all hydrogen; and

b) when Z is $-R^2$, then at least one of V, W, and W' is not hydrogen, alkyl, aralkyl, or alicyclic; and

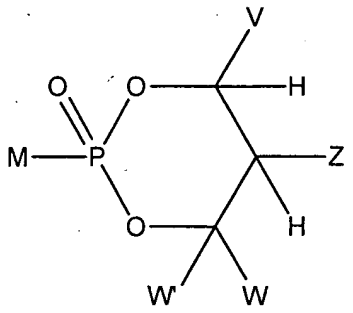
M is selected from the group that, attached to PO_3^{2-}, $P_2O_6^{3-}$, or $P_3O_9^{4-}$, is biologically active *in vivo* and that is attached to the phosphorus atom in Formula I via an oxygen atom, with the proviso that MPO_3^{2-} is not an FBPase inhibitor;

wherein said compound of Formula I is converted to MPO_3H_2 by human liver microsomes;

pharmaceutically acceptable prodrugs and salts of Formula I;

and a pharmaceutically acceptable excipient.

182. (Previously added) A pharmaceutical composition comprising a compound of Formula I:



Formula I

wherein:

V, W and W' are independently selected from the group consisting of hydrogen, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 atoms, wherein the cyclic group optionally contains one heteroatom and is substituted with a hydroxy, acyloxy, alkoxycarbonyloxy, or aryloxycarbonyloxy group attached to a carbon atom that is three atoms away from both oxygen atoms that are attached to the phosphorus atom; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group wherein the cyclic group optionally contains one heteroatom, and is fused to an aryl group, at the beta and gamma position to the oxygen attached to the phosphorus; or

together V and W are connected via an additional three carbon atoms to form an optionally substituted cyclic group containing six carbon atoms and is optionally substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxycarbonyloxy, alkylthiocarbonyloxy, and aryloxycarbonyloxy groups, wherein such substituent is attached to one of said carbon atoms that is three atoms away from an oxygen attached to the phosphorus atom; or

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

together W and W' are connected via an additional 2-5 atoms to form a cyclic group, optionally containing 0-2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl; or

Z is selected from $-CHR^2OH$, $-CHR^2OC(O)R^3$, $-CHR^2OC(S)R^3$, $-CHR^2OC(S)OR^3$, $-CHR^2OC(O)SR^3$, $-CHR^2OCO_2R^3$, $-OR^2$, $-SR^2$, $-CHR^2N_3$, $-CH_2$(aryl), -CH(aryl)OH, $-CH(CH=CR^2_2)OH$, $-CH(C\equiv CR^2)OH$, $-R^2$, $-NR^2_2$, $-OC(O)R^3$, $-OCO_2R^3$, $-SC(O)R^3$, $-SCO_2R^3$, $-NHC(O)R^2$, $-NHCO_2R^3$, $-CH_2NH$(aryl), $-(CH_2)_pOR^{12}$, and $-(CH_2)_pSR^{12}$;

R^2 is selected from the group consisting of R^3 and hydrogen;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

R^{12} is selected from the group consisting of hydrogen, and lower acyl; and

p is an interger 2 or 3;

with the provisos that:

a) V, Z, W, and W' are not all hydrogen; and

b) when Z is $-R^2$, then at least one of V, W, and W' is not hydrogen, alkyl, aralkyl, or alicyclic; and

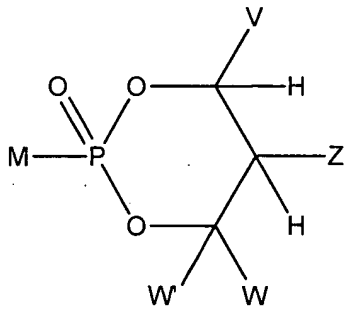
M is selected from the group that, attached to PO_3^{2-}, $P_2O_6^{3-}$, or $P_3O_9^{4-}$, is biologically active *in vivo* and that is attached to the phosphorus atom in Formula I via a nitrogen atom, with the proviso that MPO_3^{2-} is not an FBPase inhibitor;

wherein said compound of Formula I is converted to MPO_3H_2 by human liver microsomes;

pharmaceutically acceptable prodrugs and salts of Formula I;

and a pharmaceutically acceptable excipient.

183. (Currently amended) A pharmaceutical composition comprising a compound of Formula I:



Formula I

wherein:

W and W' are independently selected from the group of H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl;

V is selected from the group of aryl, substituted aryl, heteroaryl, substituted heteroaryl, alkynyl and 1-alkenyl;

Z is selected from $-CHR^2OH$, $-CHR^2OC(O)R^3$, $-CHR^2OC(S)R^3$, $-CHR^2OC(S)OR^3$, $-CHR^2OC(O)SR^3$, $-CHR^2OCO_2R^3$, $-OR^2$, $-SR^2$, $-CHR^2N_3$, $-CH_2$(aryl), $-CH$(aryl)OH, $-CH(CH{=}CR^2_2)OH$, $-CH(C{\equiv}CR^2)OH$, $-R^2$, $-NR^2_2$, $-OC(O)R^3$, $-OCO_2R^3$, $-SC(O)R^3$, $-SCO_2R^3$, $-NHC(O)R^2$, $-NHCO_2R^3$, $-CH_2NH$(aryl), $-(CH_2)_pOR^{12}$, and $-(CH_2)_pSR^{12}$; or

together V and Z are connected via 3-5 atoms to form a cyclic group, optionally containing 1 heteroatom, that is fused to an aryl group at the beta and gamma position to the oxygen attached to the phosphorus;

p is an integer 2 or 3;

R^2 is selected from the group of R^3 and –H;

R^3 is selected from the group of alkyl, aryl, alicyclic, and aralkyl;

R^{12} is selected from the group consisting of hydrogen, and lower acyl; and

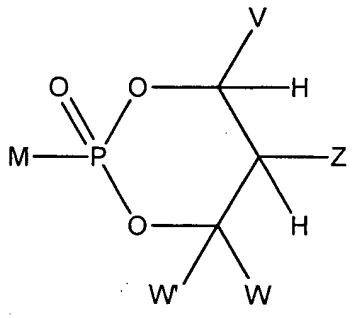
M is selected from the group that, attached to PO_3^{2-}, $P_2O_6^{3-}$, or $P_3O_9^{4-}$, is biologically active *in vivo* and that is attached to the phosphorus atom in Formula I via a carbon, oxygen, or nitrogen atom;

wherein said compound of formula I is converted to MPO_3H_2 by human liver microsomes, with the proviso that M-PO_3^{2-} is not an FBPase inhibitor;

pharmaceutically acceptable prodrugs and salts of Formula I;

and a pharmaceutically acceptable excipient.

184. (Currently amended) A pharmaceutical composition comprising a compound of Formula I:



Formula I

wherein:

V, W and W' are independently selected from the group of –H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl;

Z is selected from the group of: $-CHR^2OH$, $-CHR^2OC(O)R^3$, $-CHR^2OC(S)R^3$, $-CHR^2OCO_2R^3$, $-CHR^2OC(O)SR^3$, $-CHR^2OC(S)OR^3$, $-CH(aryl)OH$, $-CH(CH=CR^2_2)OH$, $-CH(C\equiv CR^2)OH$, $-SR^2$, $-CH_2NHaryl$, $-CH_2$ aryl; or

together V and Z are connected via 3-5 carbon atoms to form a cyclic group, optionally containing heteroatom, substituted with hydroxy, acyloxy, alkoxycarbonyloxy, or aryloxycarbonyloxy attached to a carbon atom that is three atoms from an oxygen attached to phosphorus;

R^2 is selected from the group of R^3 and H;

R^3 is selected from the group of alkyl, aryl, alicyclic, and aralkyl; and

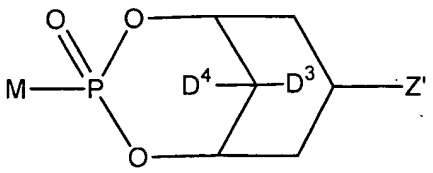
M is selected from the group that, attached to PO_3^{2-}, $P_2O_6^{3-}$, or $P_3O_9^{4-}$, is biologically active *in vivo* and that is attached to the phosphorus atom in Formula I via a carbon, oxygen, or nitrogen atom;

wherein said compound of formula I is converted to MPO_3H_2 by human liver microsomes, with the proviso that $M\text{-}PO_3^{2-}$ is not an FBPase inhibitor

pharmaceutically acceptable prodrugs and salts of Formula I;

and a pharmaceutically acceptable excipient.

185. (Currently amended) A pharmaceutical composition comprising a compound of Formula VIII:



VIII

wherein:

Z' is selected from the group of –OH, $-OC(O)R^3$, $-OCO_2R^3$, and $-OC(O)SR^3$;

D^4 and D^3 are independently selected from the group of –H, alkyl, $-OR^2$, –OH, and $-OC(O)R^3$; with the proviso that at least one of D^4 and D^3 are –H;

R^2 is selected from the group of R^3 and H;

R^3 is selected from the group of alkyl, aryl, alicyclic, and aralkyl; and

M is selected from the group that, attached to PO_3^{2-}, $P_2O_6^{3-}$, or $P_3O_9^{4-}$, is biologically active *in vivo* and that is attached to the phosphorus atom in Formula I via a carbon, oxygen, or nitrogen atom;

wherein said compound of formula I is converted to MPO_3H_2 by human liver microsomes, with the proviso that $M\text{-}PO_3^{2-}$ is not an FBPase inhibitor;

and pharmaceutically acceptable prodrugs and salts of Formula VIII;

and a pharmaceutically acceptable excipient.--

REMARKS

Claims 168-185 are pending. Claims 183-185 have been amended. No new matter was added to the claims. Support for the amendments can be found throughout the specification, for example at p. 21, lines 8-10.

All pending claims stand rejected. The Examiner also notes that claims 168-185 are distinguished over the prior art of record.

All of the above changes are cosmetic and none raise any issue of patentability. Both before and after the above changes, the invention was described in full, clear, concise, and exact terms and met all conditions for patentability under 35 USC 101 *et seq*. The scope of the claims of any resulting patent (and any and all limitations in any of said claims) shall not under any circumstances be limited to their literal terms, but are intended to embrace all equivalents. Accordingly, under no circumstances whatsoever may these claims be interpreted as:

- having been altered in any way for any reason related to patentability;
- having been narrowed;
- a concession that the invention as patented does not reach as far as the original, unamended claim;
- a surrender of any subject matter as a condition of receiving a patent; and/or, estopping applicants from asserting infringement against every equivalent, whether now known or later developed, foreseen or unforeseen;

Applicants also emphasize that the decision to address the Examiner's suggestions via claim amendment with the understandings set forth above is not in any way intended to avoid the "gatekeeping" role of the PTO with regard to the examination and issuance of valid patents for patentable inventions.

I. ELECTION

The Examiner acknowledges Applicants election with traverse of the species of Formula I wherein MH is araC; Z, W, and W' are hydrogen; and V is 4-pyridyl. The Examiner also notes that the full scope of claims 168-185 have been examined.

II. STATUTORY DOUBLE PATENTING

The Examiner has rejected claims 168 and 180-185 under 35 U.S.C. § 101 as claiming the same invention as that of claims 95 and 168-173 of U.S. Patent No. 6,312,662.

The Applicants respectfully traverse this rejection.

Claims 95 and 168-173 of U.S. Patent No. 6,312,662 are compound claims, while the current claims are all pharmaceutical composition claims. It is also noted that the current claims require an additional limitation, "a pharmaceutically acceptable excipient." Therefore, claims 168 and 180-185 of the current application do not claim the same invention as claimed in claims 95 and 168-173 of U.S. Patent No. 6,312,662.

In view of the above, the Applicants respectfully request that the Examiner withdraw the statutory double patenting rejection.

III. OBVIOUSNESS TYPE DOUBLE PATENTING

The Examiner has rejected claims 168-179 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 95-130 of U.S. Patent No. 6,312,662.

The Applicants are filing a properly executed terminal disclaimer along with this communication. As such, the Applicants respectfully request withdrawal of the double patenting rejection.

IV. 35 USC § 112 REJECTIONS, SECOND PARAGRAPH

A. Claims 169-173 and 177-179

The Examiner has rejected claims 169-173 and 177-179 under 35 USC § 112, second paragraph as indefinite. The Examiner finds that the claims are ambiguous because "Applicant refers to the variable MH in Formula I, but there is no variable MH in Formula I. However, there is a variable M attached to the phosphorus in Formula A. Did the Applicant intend MH to be M?" (Office Action p. 4)

The Applicants respectfully traverse this rejection.

The Applicants did intend to use the term "MH." The Applicants note that the specification at p. 21, lines 1-7 explains the relationship of M and MH:

> The term "parent drug" refers to MH for phosph(oramid)ates where M is connected to –P(O)(OR)(OR) via oxygen, sulfur, or nitrogen, and M-PO_3^{2-} when M is connected to –P(O)(OR)(OR) via carbon. For example, AZT can be thought of as a parent drug in the form of MH. In the body AZT is first phosphorylated to AZT-PO_3^{2-} and then further phosphorylated to form AZT-triphosphate, which is the biologically active form. The parent drug form MH only applies when M is attached via N, S or O. In the case of PMEA, the parent drug form is M-PO_3^{2-}.
> (specification p. 21, lines 1-7)

MH clearly refers to the parent drug. The parent drug MH is phosphorylated to become the biologically active drug. (*see* specification pp. 37-38).

Given the teaching in the specification, a person of ordinary skill in the art would not find the claims ambiguous and would have no difficulty in determining the scope of the claims. Therefore, the Applicants respectfully request that the Examiner withdraw the indefiniteness rejection.

B. Claims 183, 184, and 185

The Examiner has rejected claims 183, 184, and 185 under 35 USC § 112, second paragraph as indefinite. The Examiner argues that the claims are ambiguous "because the variable M in formula 1 has not been defined. In addition, M (see lines 20 and 21) has not been defined in MPO3H2 and MPO32-." (Office Action pp. 4-5)

The Examiner also notes that "the claims were examined as if M is attached to the phosphorus of Formula I via a carbon, oxygen, or nitrogen atom." (Office Action p. 5)

The Applicants respectfully traverse this rejection, as the Applicants believe that a person of ordinary skill in the art would be able to determine what M compounds are claimed by the present invention. However, in order to advance the prosecution of this application, the Applicants have amended claim 183-185 to further clarify the use of the term "M" in the claim.

In view of the above, the Applicants respectfully request that the Examiner withdraw the indefiniteness rejection.

C. Claims 168 and 180-182

The Examiner has rejected claims 168 and 180-182 under 35 USC § 112, second paragraph as indefinite. The Examiner contends that the claims are "confusing because of the proviso that 'V, Z, W, and W' are not all hydrogen'. In particular, the phrase is confusing because Z cannot be hydrogen (see definition of the variable Z)." (Office Action p. 5)

The Applicants respectfully traverse this rejection.

The claims in question define Z as "Z is selected from ...-R^2..." and R^2 can be hydrogen. Therefore the Applicants believe that the proviso is not redundant or confusing.

In view of the above, the Applicants respectfully request that the Examiner withdraw the indefiniteness rejection.

CONCLUSION

In view of the foregoing remarks, it is believed that the application is in condition for allowance, and such action is respectfully requested at the Examiner's earliest convenience.

Respectfully submitted,

Dated: 10/1/03

By: Diana L Bush

Diana L. Bush, Ph.D.
Reg. No. 51,109

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Patent
45198.00027.CON1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: **Erion *et al.***	
Serial No.: **09/978,454**	Group Art Unit: **1616**
Filed: **October 15, 2001**	Examiner: **Dameron Jones**
Title: ***NOVEL PRODRUGS FOR PHOSPHORUS-CONTAINING COMPOUNDS***	

TERMINAL DISCLAIMER UNDER 37 C.F.R. §1.321(B)

Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Metabasis Therapeutics, Inc., a corporation duly organized under the laws of the State of Delaware, having a principal office located at 9390 Towne Centre Drive, San Diego, California 92121, and duly represented by the undersigned, represents that it is the assignee of the full title and interest in and to the above-identified Application Serial No. 09/978,454, filed October 15,

CERTIFICATE OF TRANSMISSION
(37 C.F.R. §1.8)

I hereby certify that this paper (along with anything referred to as being attached or enclosed) is being facsimile transmitted to the United States Patent and Trademark Office on the date shown below.

Jill C. Youkel
Name of Person Transmitting Paper

October 1, 2003
Date of Transmission

Signature of Person Transmitting Paper

2001, as evidenced by the deed of Assignment recorded on October 15, 2001 at Reel 012264, Frame 0962.

Metabasis Therapeutics, Inc., hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on Application Serial 09/978,454 which would extend beyond the expiration date of the full statutory term of prior U.S. Patent No. 6,312,662, the term being defined in 35 U.S.C. 154 to 156. Metabasis Therapeutics, Inc. hereby agrees that any patent granted on Application Serial No. 09/978,454 shall be enforceable only for and during such period that such patent and prior U.S. Patent No. 6,312,662, are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, Metabasis Therapeutics, Inc. does not disclaim the terminal part of any patent granted on the instant application that would extend to the expiration date of the full statutory term as defined in 35 U.S.C. 154 to 156 of U.S. Patent No. 6,312,662, as presently shortened by any terminal disclaimer filed, in the event that it later: expires for failure to pay a maintenance fee, is held unenforceable, is found invalid by a court of competent jurisdiction, is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321, has all claims canceled by a reexamination certificate, is reissued, or is in any manner terminated prior to the expiration of its full statutory term as presently shortened by any terminal disclaimer.

I hereby declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further, that these statements are made with the knowledge that willful false statements, and the like so made, are punishable by fine or imprisonment, or both, under Section 1001, Title 18 of the United States

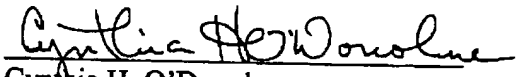
Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

The undersigned is an agent of record.

The Commissioner is hereby authorized to charge Deposit Account No. 50-2613 for the fee due herein and any other fees that may become due or credit become payable during the pendency of this application.

Respectfully submitted,

Dated: October 1, 2003

By: 

Cynthia H. O'Donohue
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